# The Hofmann Rearrangement. III. Kinetic Substituent Effects of 4- and 5-Substituted 2-Chloro-*N*-chlorobenzamides

Tsuneo IMAMOTO, Yuho TSUNO, and Yasuhide YUKAWA

*The Institute of Scientific and Industrial Research, Osaka University, Yamadakami, Suita, Osaka*

(Received September 25, 1970)

The kinetic measurements of the Hofmann rearrangement of 2,4-, 2,5- 2,6-, and 3,5-disubstituted *N*-chlorobenzamides were carried out. The rate constants of 4- and 5-substituted 2-chloro-*N*-chlorobenzamides were applicable to the LArSR relationship:

$$\log k/k_0 = -2.21(\sigma^0+0.69\Delta\bar{\sigma}_R^+) + 0.03$$

indicating that the reactivity of the 2-chloro series was subjected to a larger additional conjugation effect than that of the 2-unsubstituted series. The detailed discussion of the reaction mechanism on the basis of these results supported strongly the concerted mechanism.

As has been described in the preceding papers,[1,2] kinetic studies of the Hofmann rearrangement of *mono*-substituted *N*-bromo- and *N*-chloro-benzamides were carried out with a view to elucidating its precise reaction mechanism. From the results, we concluded that both the bond-energy effect in the initial state and the participation of the migrating phenyl group in electron-deficient nitrogen in the transition state were important factors in characterizing the rearrangement.

In order to establish the existence of the above two factors, a kinetic study of the rearrangement of 4- and 5-substituted 2-chloro-*N*-chlorobenzamides has undertaken, and a further attempt has been made to evaluate each of them semi-quantitatively on the basis of LFER.

In this paper we will report these kinetic results, along with those of a few other disubstituted *N*-chlorobenzamides, and will discuss the reaction mechanism of the Hofmann rearrangement.

## Experimental

*Materials.* *Disubstituted benzamides* were prepared by the usual methods and were identified by elementary analysis. The melting points of these amides are listed in Table 1.

*Disubstituted N-chlorobenzamides* were prepared by the methods described in the preceding paper. The melting points and the analytical data of these *N*-chloroamides are listed in Table 1.

*Kinetic Measurements.* The reaction rates were deter-

TABLE 1. DISUBSTITUTED BENZAMIDES AND THEIR *N*-CHLORO-DERIVATIVES

| Subst. | Amides Mp °C | *N*-Chloroamides Mp °C (lit a)) | Analysis (Calcd) C% | H% | N% | Cl% | Act. Cl% |
|---|---|---|---|---|---|---|---|
| 2-Cl-4-$CH_3O$ | 161.5—162.5 | 128.5—129.0 | 43.63 | 3.33 | 6.29 | 32.33 | 16.28 |
| | | | (43.67) | (3.21) | (6.37) | (32.22) | (16.11) |
| 2-Cl-4-$CH_3$ | 180—181 | 119—120 | 47.06 | 3.45 | 6.84 | 34.58 | 17.21 |
| | | | (47.09) | (3.46) | (6.86) | (34.75) | (17.37) |
| 2-Cl-5-$CH_3$ | 185.5—186.0 | 121—122 | 46.88 | 3.39 | 6.83 | 34.62 | 17.13 |
| | | | (47.09) | (3.46) | (6.86) | (34.75) | (17.37) |
| 2,4-di-Cl | 193—194 | 136—137 | 37.41 | 1.71 | 6.13 | 47.20 | 15.79 |
| | | | (37.46) | (1.80) | (6.24) | (47.38) | (15.79) |
| 2,5-di-Cl | 160.0—160.5 | 158.0—158.5 | 37.29 | 1.77 | 6.00 | 47.20 | 15.64 |
| | | | (37.46) | (1.80) | (6.24) | (47.38) | (15.79) |
| 2-Cl-4-$NO_2$ | 171.0—171.5 | 190—200 | 35.97 | 1.67 | 12.19 | 30.24 | 14.56 |
| | | (184—185) | (35.77) | (1.72) | (11.92) | (30.17) | (15.08) |
| 2,6-di-Cl | 202—203 | 190—192 | 37.52 | 1.87 | 6.42 | 47.50 | 15.64 |
| | | | (37.46) | (1.80) | (6.33) | (47.38) | (15.79) |
| 3,5-di-Cl | 161—162 | 198—200 | 37.59 | 1.71 | 6.33 | 47.20 | 15.44 |
| | | | (37.46) | (1.80) | (6.33) | (47.38) | (15.79) |
| 3,5-di-Br | 187—188 | 212—214 | 26.75 | 1.23 | 4.26 | | 11.38 |
| | | | (26.83) | (1.29) | (4.47) | | (11.31) |
| 3,5-di-$NO_2$ | 183—184 | 176—177 | 34.26 | 1.44 | 17.28 | 14.31 | 14.16 |
| | | (168) | (34.23) | (1.64) | (17·11) | (14.44) | (14.44) |
| 2,5-di-Cl-4-$CH_3$ b) | | 171—173 | 40.14 | 2.30 | 5.85 | 44.45 | 14.77 |
| | | | (40.29) | (2.54) | (5.87) | (44.59) | (14.86) |

a) B. Altenkirk and S. S. Israelstam, *J. Org. Chem.*, **27**, 4532 (1962).

b) This *N*-chloroamide was obtained by the treatment of 2-chloro-4-methylbenzamide with chlorine gas under the same reaction condition as applied for the other amides.

---

[1] T. Imamoto, Y. Tsuno, and Y. Yukawa, This Bulletin, **44**, 1632 (1971).

[2] T. Imamoto, Y. Tsuno, and Y. Yukawa, *ibid.*, **44**, 1639 (1971).

mined according to the procedure described in the preceding paper. The initial concentrations of *N*-chloroamide and sodium hydroxide employed were 0.025 mol/*l* and 0.5 N respectively.

## Results and Discussion

The rates of the release of the chloride ion from the conjugate bases of *multi*-substituted *N*-chlorobenzamides were measured under the same reaction conditions as those used in connection with the preceding kinetics of *mono*-substituted *N*-chlorobenzamides. All the runs except those of the 3,5-dinitro derivative strictly obeyed first-order kinetics, at least to 75% completion of the reaction.[3] The reproducibility of the rate constant from repeated runs was within 0.7%, and the plots of log *k*/*T* *vs.* 1/*T* gave an excellent straight line in every case. The observed first-order rate constants are listed in Table 2. The rate constants at 30.00°C and the derived activation parameters are summarized in Table 3.

TABLE 2. RATE CONSTANTS OF THE HOFMANN REARRANGEMENT OF *multi*-SUBSTITUTED *N*-CHLOROBENZAMIDES

| Subst. | Temp. °C | $k_1 \times 10^4$ (sec$^{-1}$) |
|---|---|---|
| 2-Cl-4-$CH_3O$ | 6.00 | 6.52 ± 0.02 |
| | 4.00 | 4.680 ± 0.013 |
| | 0.00 | 2.366 ± 0.004 |
| 2-Cl-4-$CH_3$ | 17.00 | 6.478 ± 0.016 |
| | 13.00 | 3.358 ± 0.006 |
| | 10.00 | 2.021 ± 0.005 |
| | 5.00 | 0.8459 ± 0.0016 |
| | 0.00 | 0.4995 ± 0.0011 |
| 2-Cl-5-$CH_3$ | 20.00 | 4.495 ± 0.008 |
| | 15.00 | 1.976 ± 0.002 |
| | 10.00 | 0.8443 ± 0.0016 |
| | 0.00 | 0.3495 ± 0.0003 |
| 2,4-di-Cl | 30.00 | 5.446 ± 0.001 |
| | 25.00 | 2.502 ± 0.002 |
| | 20.00 | 1.118 ± 0.002 |
| | 15.00 | 0.4822 ± 0.00004 |
| 2,5-di-Cl | 35.00 | 4.406 ± 0.003 |
| | 30.00 | 2.059 ± 0.001 |
| | 25.00 | 0.9309 ± 0.0005 |
| | 20.00 | 0.4089 ± 0.0007 |
| 2-Cl-4-$NO_2$ | 45.00 | 2.755 ± 0.006 |
| | 40.00 | 1.311 ± 0.002 |
| | 35.00 | 0.5979 ± 0.0006 |
| | 30.00 | 0.2675 ± 0.0003 |
| 2,6-di-Cl | 35.00 | 6.191 ± 0.007 |
| | 30.00 | 2.829 ± 0.002 |
| | 25.00 | 1.259 ± 0.0009 |
| | 20.00 | 0.5453 ± 0.0003 |
| | 15.00 | 0.2270 ± 0.0002 |
| 3,5-di-Cl | 50.00 | 3.274 ± 0.005 |
| | 45.00 | 1.634 ± 0.001 |
| | 40.00 | 0.7902 ± 0.0007 |
| | 30.00 | 0.1715 ± 0.0002 |
| 3,5-di-Br | 50.00 | 3.924 ± 0.004 |
| | 45.00 | 1.952 ± 0.002 |
| | 40.00 | 0.9545 ± 0.0008 |
| | 30.00 | 0.2084 ± 0.0003 |
| 2,5-di-Cl-4-$CH_3$ | 30.00 | 7.23 ± 0.01 |
| | 25.00 | 3.354 ± 0.004 |
| | 20.00 | 1.518 ± 0.002 |
| | 15.00 | 0.6620 ± 0.0009 |

TABLE 3. KINETIC RESULTS OF THE HOFMANN REARRANGEMENT OF *multi*-SUBSTITUTED *N*-CHLOROBENZAMIDES

| Subst. | $k_1 \times 10^4$ (sec$^{-1}$) | $\Delta H^{\neq}$ (kcal/mol) | $\Delta S^{\neq}$ (e. u.) |
|---|---|---|---|
| 2-Cl-4-$CH_3O$ | 253[a)] | 25.05±0.14 | 16.8 ±0.47 |
| 2-Cl-4-$CH_3$ | 48.8[a)] | 26.57±0.03 | 18.52±0.11 |
| 2-Cl-5-$CH_3$ | 21.46[a)] | 27.02±0.01 | 18.37±0.03 |
| 2,4-di-Cl | 5.446 | 27.44±0.04 | 17.04±0.14 |
| 2,5-di-Cl | 2.059 | 27.86±0.05 | 16.48±0.16 |
| 2-Cl-4-$NO_2$ | 0.2675 | 29.19±0.06 | 16.82±0.21 |
| 2,6-di-Cl | 2.829 | 28.55±0.04 | 19.39±0.12 |
| 3,5-di-Cl | 0.1715 | 28.10±0.04 | 12.33±0.14 |
| 3,5-di-Br | 0.2084 | 27.94±0.03 | 12.20±0.11 |
| 2,5-di-Cl-4-$CH_3$ | 7.226 | 27.04±0.05 | 16.29±0.15 |

a) Extrapolated from data at other temperatures.

As a result of the previous kinetic studies of the Hofmann rearrangement of *mono*-substituted *N*-bromo- and *N*-chloro-benzamides, it was suggested that the bond-energy effect in the initial state and the participation of the phenyl group in electron-deficient nitrogen were important factors in controlling the reactivity. The most interesting point in connection with these two factors consists in the effects of the *para*-substituted electron-releasing conjugative groups on the reactivity. In the transition state these substituents facilitate the additional conjugation of the phenyl group with electron-deficient nitrogen, with a considerable stabilization of its state. In the inital state, however, such substituents increase the bond-order of the nitrogen-halogen bond through the cross-conjugation of the carbonyl group with the phenyl group and with the nitrogen orbital, and lead to a rate retardation with a stabilization of the initial state. The former conjugation effect is expected to give a comparatively large positive value of the reasonance parameter, *r*, of the LArSR relationship, whereas the latter effect will rather afford a negative *r*-value. The resonance parameter ($r$=0.41) for the rearrangement of *mono*-substituted *N*-chlorobenzamides can be qualitatively interpreted in terms of the mutual compensation of the conjugation effects in the initial and the transition states.

In order to establish these theories, it is necessary to ascertain the substituent effect in a system where the amide group is sufficiently hindered from conjugating with the phenyl group in the initial state, and so the kinetic study of 4- and 5-substituted 2-chloro-*N*-chlorobenzamides has been undertaken. The chloro group at the *ortho*-position has been chosen as the most suitable group in satisfying the following requirements: sufficient steric effect to restrict the through-conjugation of the amide group with the phenyl group in the initial state, measurable rates, and the easily-

---

[3] In the case of 3,5-dinitro derivative excellent first-order plots were not obtained especially at the temperature lower than 45°C. This anomaly is presumably caused by accompanying the hydrolysis of the reactant conjugate base of *N*-chloroamide.

available amides.

The logarithms of the relative rate constants of the present 2-chloro series have been plotted against those of the preceding 2-unsubstituted series. As is illustrated in Fig. 1, all the *meta*-substituents and the *para*-nitro substituent form an excellent strainght line with a slope of 0.930 and a correlation coefficient of 0.9999, whereas the electron-releasing conjugative substituents at the *para*-position deviate upward from the correlation line. Each deviation, however, appears to be proportional to electron-releasing conjugative ability of its substituent. In fact, the least-mean-square calculation using the values of the electron-releasing conjugative ability ($\Delta\bar{\sigma}_R^+$)[4] gives an excellent straight line with a correlation coefficient of 0.9999, including all the *para*-substituents, as is shown in Fig. 2. The slope of the correlation line is 0.930, which is the same as that calculated from all the *meta*-substituents and the *para*-nitro substituent. This fact evidently indicates that the reactivity of the 2-chloro series is subjected to a larger additional conjugation effect than that of the 2-unsubstituted series. The application of the LArSR relationship to the present data gives a good linearity, as is shown in Fig. 3. Although the calculated reaction

$$\log k/k_0 = -2.21(\sigma^0+0.69\Delta\bar{\sigma}_R^+) + 0.03$$

constant ($\rho=-2.21$) is nearly equal to the value of the 2-unsubstituted series ($\rho=-2.43$), the resonance parameter ($r=0.69$) is considerably larger than that of the 2-unsubstituted series ($r=0.41$).

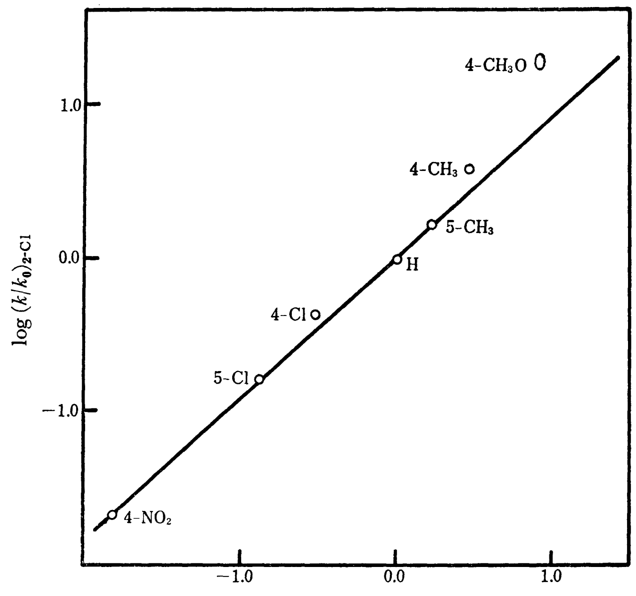


Fig. 1. Comparison with 2-unsubstituted derivatives.

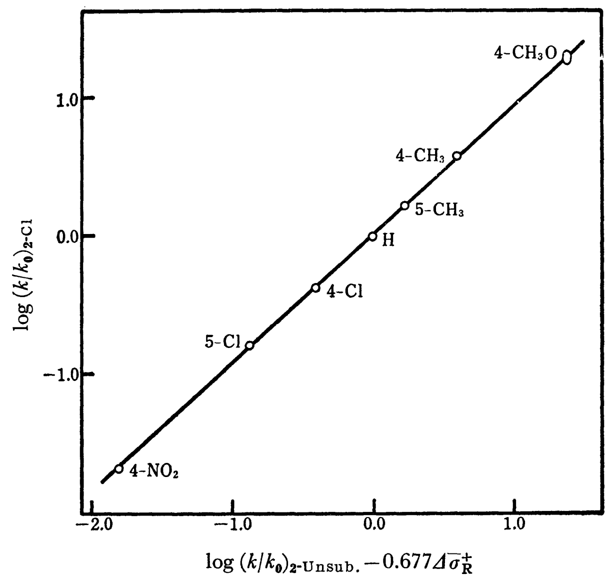


Fig. 2. Comparison with 2-unsubstituted derivatives with the application of the LArSR relationship.

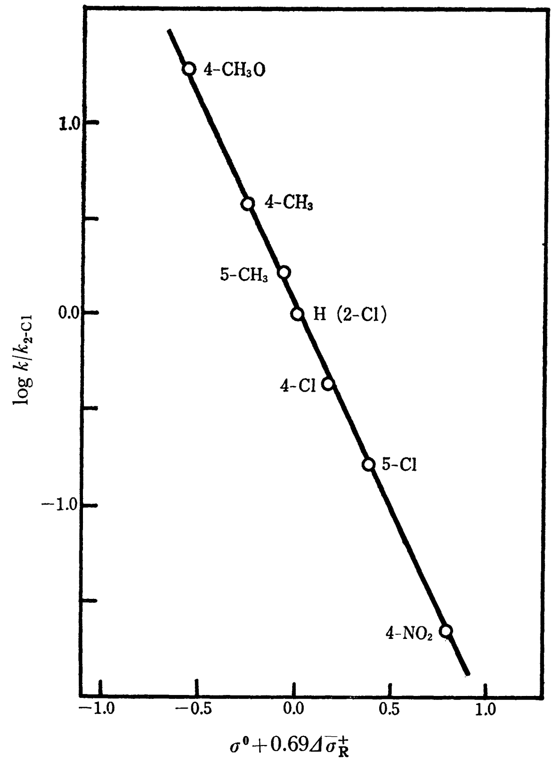
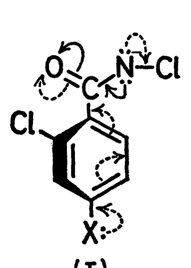
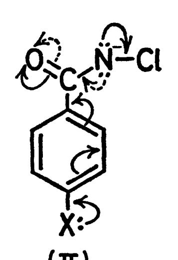


Fig. 3. Application of the LArSR relationship.

The conjugations applicable to the initial state are visualized in Formulae (I) and (II). The through-conjugation of the carbonyl group with the phenyl



(I)



(II)

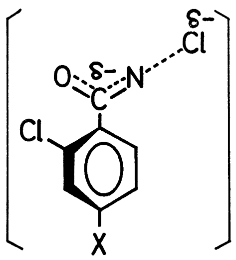
group is remarkably restricted in the 2-chloro system (I), while it is not in the 2-unsubstituted system (II). The substituent effect on this conjugation effect in the 2-chloro series, therefore, is expected to be

---

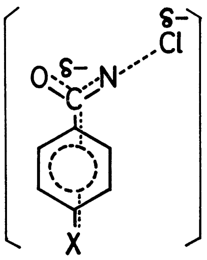
[4] Y. Yukawa, Y. Tsuno, and M. Sawada, This Bulletin, **39**, 2274 (1966).

smaller than that in the 2-unsubstituted series.

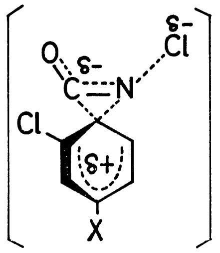
On the other hand, in the transition state the degree of the conjugation in both series depends on the reaction mechanism (or on the structure of the transition state). In the two-step mechanism, the conjugation of phenyl group with the amide group is restricted in the 2-chloro system (III), but not in the 2-unsubstituted system (IV). On the contrary, in the concerted mechanism the degree of the conjugation may be expected to be almost the same for both the 2-chloro and 2-unsubstituted systems (V and VI), since in this state the phenyl ring is twisted almost at a right angle to the amide group due to the effective overlap of orbitals.



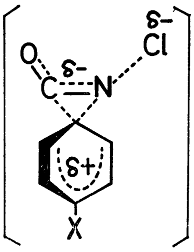
(III)



(IV)



(V)



(VI)

If the reaction proceeds through the two-step mechanism, the reactivity of the 2-chloro series should be considerably affected by the steric restriction of the conjugation in both the initial and transition states. The substituent effect of the conjugation effect on the 2-chloro series is expected to be smaller than that on the 2-unsubstituted series; the *r*-value of the 2-chloro series should be smaller than the value (0.41) of the 2-unsubstituted series. On the other hand, if the reaction proceeds through the concerted mechanism, the *r*-value to be observed on the 2-chloro series will be larger than the value of the 2-unsubstituted series, since the effect of the conjugation in the transition state is almost the same for both the 2-chloro and 2-unsubstituted series; further, the substituent effect on the conjugation effect in the initial state is reduced for the 2-chloro series more than for the 2-unsubstituted series. The comparatively large positive *r*-value (0.69) resulting in the 2-chloro series strongly supports the concerted mechanism rather than the two-step mechanism.

It is of interest to discuss the effect of the introduction of the chlorine atom into the *ortho*-position in relation to the above discussion of the substituent effect of 4- and 5-substituted 2-chloro-*N*-chlorobenzamides. The relative reactivities among unsubstituted, 2-chloro, 4-chloro, 2,4-dichloro, and 2,6-dichloro derivatives are listed in Table 4. The first introduction of the chlorine atom at the *ortho*-position effects a small rate acceleration ($k_{2-\text{Cl}}/k_{\text{H}}=1.6$), where as the second one at another *ortho*-position effects rather a rate retardation ($k_{2,6-\text{diCl}}/k_{2-\text{Cl}}=0.22$). The steric rate effect of the *ortho*-substituent can be qualitatively evaluated by means of the *ortho*/*para* rate ratios, since the polar effect of the *ortho*-substituent is generally recognized to be nearly equal to that of the corresponding *para*-substituent. The $k_{2-\text{Cl}}/k_{4-\text{Cl}}$ value of the present reaction is calculated to be 5.3, indicating considerable steric rate acceleration due to the first introduction of the *ortho*-chloro substituent. The value of $k_{2,6-\text{diCl}}/k_{2,4-\text{diCl}}$, which corresponds to the steric rate effect due to the other *o*-chloro substituent, is calculated to be 0.52, indicating that the steric effect of the other *o*-chloro substituent affords a rather small rate retardation.

Table 4.

$k_{2-\text{Cl}}/k_{\text{H}} = 1.6$
$k_{2,6\text{-di-Cl}}/k_{\text{H}} = 0.35$
$k_{2,6\text{-di-Cl}}/k_{2\text{-Cl}} = 0.22$
$k_{2\text{-Cl}}/k_{4\text{-Cl}} = 5.3$
$k_{2,6\text{-di-Cl}}/k_{2,4\text{-di-Cl}} = 0.52$

From these results, it would be reasonable to consider that the first introduction of the chloro substituent at the *ortho*-position effects a large steric effect to restrict the conjugation of the phenyl group with the carbonyl group considerably. The observed value of the resonance parameter of the 2-chloro series, therefore, may be attributed for the most part to the conjugation effect in the transition state. This value can be compared with the *r*-value of the Beckmann rearrangement, the reaction mechanism of which is estimated to be a concerted one. The *r*-value of the Beckmann rearrangement under various conditions has been calculated to be *ca.* 0.65. If the substituent effect on the conjugation in the transition state of the Hofmann rearrangement has an *r*-value of about 0.7, the effect of the *dπ-pπ* conjugation in the initial state in the 2-unsubstituted series might be estimated to be *ca.* −0.3 as a resonance parameter by the subtraction of the value of 0.7 from the observed *r*-value (0.41) of the 2-unsubstituted series. This estimated *r*-value of the bond-energy effect due to the *dπ-pπ* conjugation of the nitrogen-chlorine bond is reasonable as compared with the observed *r*-values of the Curtius and the Wolff rearrangements, which are characterized exclusively by the bond-energy effect of the $N-N_2$ bond.[5]

It is also of interest to discuss the substituent effects on the Hofmann rearrangement in terms of the derived activation parameters. The plots of $\Delta H^{\neq}$ *vs.* $\Delta S^{\neq}$ are

---

[5] The *r*-values of the Curtius rearrangement in toluene and of the Wolff rearrangement in toluene are −1.04 and −1.7, respectively; Y. Yukawa and Y. Tsuno, *J. Amer. Chem. Soc.*, **79**, 5530 (1957); Y. Yukawa and Y. Tsuno, *ibid.*, **80**, 6346 (1958); Y. Yukawa, Y. Tsuno, and T. Ibata, This Bulletin, **40**, 2613 (1967); Y. Yukawa, Y. Tsuno, and T. Ibata, *ibid.*, **40**, 2618 (1967).

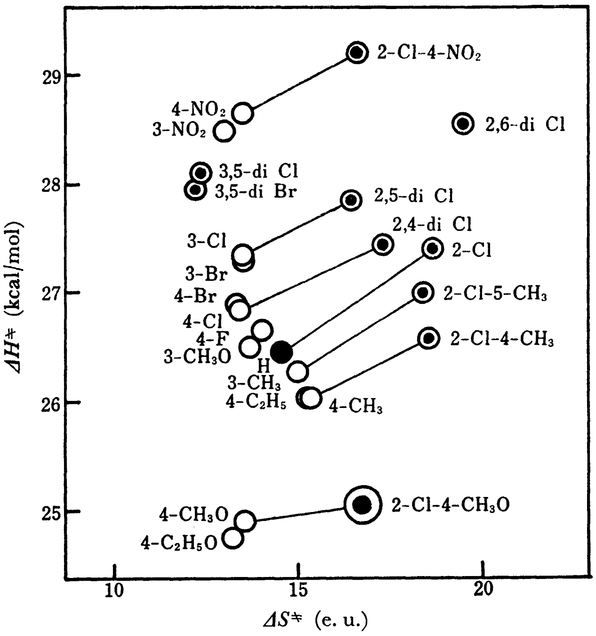


Fig. 4. $\Delta H^{\ddagger}$ *vs.* $\Delta S^{\ddagger}$ for the Hofmann rearrangement.

shown in Fig. 4, along with those of the *meta-* and *para*-substituents of the 2-unsubstituted series studied previously. In the case of the 2-unsubstituted series the enthalpy of activation varies from *ca.* 24.5 to *ca.* 28.5 kcal, although the entropy of activation varies merely from *ca.* 13 to *ca.* 15 e.u. This enthalpy dependency of the substituent effect on the reactivity is presumably caused both by the bond-energy effect in the initial state and by the additional conjugation effect of the phenyl group in the transition state, rather than by the solvation effect. The solvation effect is surely considered to play an important role in the reactivity; however, the substituent effect on it appears to be almost the same throughout the series. Another noticeable fact is shown by the plots of the 2-chloro series, which form a pattern similar to that of the 2-unsubstituted series, though they deviate in parallel fashion by *ca.* 3 e.u. and *ca.* 0.5 kcal from the corresponding plots of the 2-unsubstituted series. This fact shows that the reaction mechanism of the 2-unsubstituted and 2-chloro series are substantially the same. In the 3,5-dichloro and 3,5-dibromo derivatives, excellent additivities are found not only in the free energy of activation but also in the entropy and the enthalpy of activation. These additivities also indicate that the reaction mechanism of this rearrangement does not change with the change in the polar effect, at least not in the cases examined. The 2,6-dichloro derivative, however, does not retain any additivity. The failure of the additivity in the free energy of activation may be attributed to the entropy of activation, as is indicated in Fig. 4. The entropy gain caused by the concerted mechanism is perhaps saturated by the first introduction of the chlorine atom. The second introduction will afford rather rate retardation because of the additional polar effect.